The listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

Claim 1. (Canceled).

2. (Canceled)

3. (Canceled)

4. (Canceled)

5. (Canceled)

6. (Canceled)

7. (Canceled)

8. (Canceled)

9. (Canceled)

10. (Canceled)

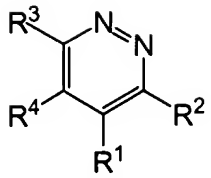
11. (Canceled)

12. (Canceled)

13. (Canceled)

14. (Currently Amended) ~~The compound of claim 13 wherein one X^1 and X^2 is N and the other of one of X^1 and X^2 is $C(R^2)$.~~

A compound of formula



or a pharmaceutically acceptable salt thereof, wherein

R^1 is C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, -C(=O)Rb, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$ or C_{1-8}alkyl substituted by 1, 2 or 3 substituents independently selected from cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^2 is C_{1-8}alkyl, phenyl, benzyl, R^c, R^f, $C_{1-4}alkylR^c$, $C_{1-4}alkylR^f$ or R^g;

R^3 is phenyl or naphthyl, each of which is substituted by 0, 1, 2 or 3 substituents selected from C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^4 is pyridyl, pyrimidinyl or triazinyl, each of which is substituted by 0, 1, 2 or 3 substituents selected from C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-NR^a(C_{1-4}alkylR^f)$, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^a is independently at each instance H or R^b;

R^b is independently at each instance C_{1-8}alkyl, phenyl or benzyl;

R^c is independently at each instance a saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 1, 2 or 3 atoms selected from N, O and S, wherein the ring is fused with 0 or 1 benzo groups and 0 or 1 saturated or unsaturated 5-, 6- or 7-membered heterocyclic ring containing 1, 2 or 3 atoms selected from N, O and S; wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups;

R^d is independently at each instance C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^{a}R^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^{a}R^a or $-NR^aC_{2-6}$alkylOR^a;

R^e is independently at each instance C_{1-6}alkyl substituted by 1, 2 or 3 substituents independently selected from R^d;

R^f is independently at each instance R^c substituted by 1, 2 or 3 substituents independently selected from R^d; and

R^g is independently at each instance R^b substituted by 1, 2 or 3 substituents independently selected from R^c, R^f and R^d.

15. (Currently Amended) The compound of claim 14 wherein

R^2 is piperidinyl, piperizinyl, morpholinyl, pyrrolidinyl, $-C_{1-8}$alkyl-piperidinyl, $-C_{1-8}$alkyl-piperizinyl, $-C_{1-8}$alkyl-morpholinyl or $-C_{1-8}$alkyl-pyrrolidinyl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from R^d;

R^3 is phenyl, substituted by 0, 1, 2 or 3 substituents selected from C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^{a}R^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^{a}R^a and $-NR^aC_{2-6}$alkylOR^a; and

R^4 is a pyridine or pyrimidine ring, optionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-NR^a(C_{1-4}$alkylR$^f)$, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^{a}R^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$,

$-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$.

16. (Currently Amended) A pharmaceutical composition comprising a compound according to Claim ~~13~~ 14 and a pharmaceutically acceptable carrier or diluent.

17. (Currently Amended) A method of treatment of rheumatoid arthritis comprising administering an effective amount of a compound according to Claim ~~13~~ 14.

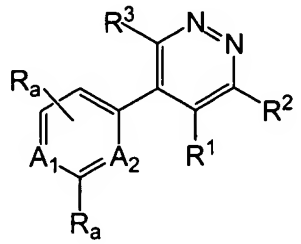
18. (Currently Amended) A method of lowering plasma concentrations of either or both TNF-α and IL-1 comprising administering an effective amount of a compound according to Claim ~~13~~ 14.

19. (Currently Amended) A method of lowering plasma concentrations of either or both IL-6 and IL-8 comprising administering an effective amount of a compound according to Claim ~~13~~ 14.

20. (Currently Amended) A method of treatment of a pain disorder in a mammal comprising administering an effective amount of a compound according to Claim ~~13~~ 14.

21. (Currently Amended) The manufacture of a medicament comprising an effective amount of a compound according to Claim ~~13~~ 14.

22. (New) A compound of Formula II



wherein

one of A^1 and A^2 is N, and the other of A^1 and A^2 is N or CR^a;

R^1 is C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, -C(=O)Rb, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$ or C_{1-8}alkyl substituted by 1, 2 or 3 substituents independently selected from cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-OR^a$ and $-SR^a$;

R^2 is piperidinyl, piperizinyl, morpholinyl, pyrrolidinyl, -C_{1-8}alkyl-piperidinyl, -C_{1-8}alkyl-piperizinyl, -C_{1-8}alkyl-morpholinyl or -C_{1-8}alkyl-pyrrolidinyl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from R^d;

R^3 is phenyl, naphthyl, pyridyl, pyrimidyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, furanyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl or benzofurnyl, each of which is substituted by 0, 1, 2 or 3 substituents selected from C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)$_2R^b$, -OC_{2-6}alkylNR^aR^a, -OC_{2-6}alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)$_2R^b$, -S(=O)$_2NR^aR^a$, -S(=O)$_2$N(R^a)C(=O)R^b, -S(=O)$_2$N(R^a)C(=O)OR^b, -S(=O)$_2$N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)$_2R^b$, -N(R^a)S(=O)$_2NR^aR^a$, -NR^aC_{2-6}alkylNR^aR^a and -NR^aC_{2-6}alkylOR^a;

R^a is independently at each instance H or R^b; and

R^b is independently at each instance C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, -C(=O) C_{1-8}alkyl, -OH, -NHC_{1-8}alkyl, -NH_2, -OC_{1-8}alkyl, -OC_{2-6}alkylNHC_{1-8}alkyl, -OC_{2-6}alkylOH, -SH, -SC_{1-8}alkyl or -N(C_{1-8}alkyl)$_2$.

23. (NEW) The compound of claim 22 wherein

each of A^1 and A^2, independently, is N;

R^1 is C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, -C(=O)Rb, -OR^a, -SR^a, -S(=O)R^b, -S(=O)$_2R^b$ or C_{1-8}alkyl substituted by 1, 2 or 3 substituents independently selected from cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -OR^a and -SR^a;

R^2 is piperidinyl, piperizinyl or pyrrolidinyl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from R^d; and

R^3 is phenyl, naphthyl, pyridyl or pyrimidyl, each of which is substituted by 0, 1, 2 or 3 substituents selected from C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, -C(=O) C_{1-8}alkyl, -C(=O)OC_{1-8}alkyl, -C(=O)OH, -C(=O)NHC_{1-8}alkyl, -C(=O)NH_2, -OH, -OC_{1-8}alkyl, -OC_{2-6}alkylNHC_{1-8}alkyl, -OC_{2-6}alkylOH, -SH, -SC_{1-8}alkyl, -S(=O)C_{1-8}alkyl, -S(=O)$_2C_{1-8}$alkyl, -S(=O)$_2NH_2$, -S(=O)$_2NHC_{1-8}$alkyl, -NH_2, -NHC_{1-8}alkyl, -N(C_{1-8}alkyl)$_2$, -N(R^a)C(=O)C_{1-8}alkyl, -N(R^a)C(=O)NHC_{1-8}alkyl or -N(R^a)S(=O)$_2C_{1-8}$alkyl.

24. (NEW) The compound of claim 22 wherein R^2 is piperidinyl or pyrrolidinyl, optionally substituted by 1, 2 or 3 substituents independently selected from R^d.

25. (NEW) A pharmaceutical composition comprising a compound according to Claim 22 and a pharmaceutically acceptable carrier or diluent.

26. (NEW) A method of treatment of rheumatoid arthritis, Pagets disease, osteoporosis, uveititis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, myocardial infarction, ischemia or reperfusion injury in a mammal, the method comprising administering an effective amount of a compound according to Claim 22 to the mammal.